

REMARKS

Claims 1-3, 5, 6, 9, 12-14, 21-24, 35, 39-41, 44-46, 51, 54, 76, and 83-85 are pending in the subject application. Claims 9, 84 and 85 are canceled herein without prejudice. Claim 1 has been amended. Claims 86-90 have been added. The amendments to claim 1 are supported by the specification and claims as filed, and no new matter is presented. Favorable reconsideration in light of the remarks which follow is respectfully requested

1. Claim Objections

Claim 9 is objected to for being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 9 has been canceled herein without prejudice. Reconsideration and withdrawal of the objection is respectfully requested.

2. 35 U.S.C. §112 Rejections

Claim 85 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Office asserts that it is not clear what alcohols are considered to meet the limitation of "short chain alcohols". Applicants believe that one of skill in the art could readily determine what is considered a short chain alcohol based on knowledge in the art and based on the specification. However, in view of the amendments made to claim 1, claim 85 has been canceled, without prejudice. Reconsideration and withdrawal of the rejection is respectfully requested.

3. 35 U.S.C. §103 Rejections

Claims 1-3, 5, 6, 9, 12-14, 21-24, 35, 39-41, 44-46, 51, 54, 76, and 83-85 are rejected under 35 U.S.C. §103(a) as being unpatentable over German Pat. No. 44 47 287 C1 in view of US Patent 5,322,685 (US '685) and Cevc et al. (Journal of Controlled Release (1997), vol. 45, pp.211-226)(Cevc).

Applicant respectfully traverses this rejection.

Applicants teach a formulation comprising penetrants that are capable of penetrating the pores of a barrier, wherein the average diameter of the penetrants is larger than that of the pores. The penetrants transport agents or enable agent penetration through the pores after the penetrants have entered the pores. The agent is selected from corticosteroids and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation. The formulation further comprises at least one antioxidant and at least one microbiocide. The antioxidant is present in an amount that reduces the increase of oxidation index to less than 100% per 6 months and is selected from the antioxidants listed in claim 1. The microbiocide is present in an amount that reduces the bacterial count of 1 million germs added per gram of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of *Pseudomonas aeruginosa* or *Staphylococcus aureus*, after a period of 4 days, and is from the microbiocides listed in claim 1.

Applicants' formulations form untradeformable vesicles (penetrants) called Transfersomes®, which are a unique drug carrier system that allows penetration of pores having a smaller average diameter than the vesicles and delivery of agents through the pores via the vesicles. Any variation in the components and compositions of the formulation can significantly impact the resulting properties of the formulation and can impact the ability of the penetrants to cross a semipermeable barrier.

As demonstrated in the enclosed declaration of Professor Gregor Cevc, Ph.D., addition of suitable antioxidants and microbiocides to such formulations is a complex matter because the penetrants are not simple carriers, but, rather, they possess properties like untradeformability that allows them to penetrate barriers like the skin. The formulation is a well-balanced system between surface-forming substances (lipids) and surface-destabilising substances, which provides the system with the characteristic deformability. However, the balance of the system can be easily compromised by even the slightest modification leading to the loss of the characteristic properties and function of the system. For example, the addition of substances like antioxidants and microbiocides can upset the balance because many antioxidants and microbiocides are not

compatible with these penetrants at all or only in specific amounts. The addition of common antioxidants and microbicides in conventional amounts, while suitable for other dermal systems, is not suitable for the present systems. In particular, the addition of such substances, even in conventional amounts, can negatively affect the properties of the penetrants by, for example, causing the penetrants to become stiff or even solubilized. This is demonstrated in the attached comparative tests which clearly show that commonly used amounts of commonly used antioxidants and microbicides can not be employed in applicants' transdermal systems, as they precipitate from the formulation, and even cause precipitation of further ingredients, which, on the one hand may lead to stiffening of the carrier, or, on the other hand, if the surface forming substances are co-precipitated, to the solubilisation of the systems. Thus, the selection of appropriate types and amounts of antioxidants and microbicides that can successfully be added to applicants' formulations is critical to adjusting a very complex well-balanced system and maintaining the well-balanced system. Such selection could not be discovered by routine experimentation.

DE'287 clearly does not teach or suggest applicants' formulations. As previously acknowledged by the Office, DE '287 does not describe a preparation wherein the agent (active substance) is a corticosteroid and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation, as claimed by applicants. Further, as previously set forth by applicants, DE'287 does not suggest such concentrations. Rather, DE'287 describes one limited situation where the more soluble component of the preparation, which applicants note would never be a corticosteroid, is present in an amount between 0.01 wt% and 15 wt%. In all other situations, the concentration is much less than applicants' claimed amount. Still further, DE '287 only generally mentions the possibility that certain antioxidants and microbicides may be used. However, DE'287 fails to teach or suggest which and how much of each substance may be successfully used without upsetting the well-balanced system of applicants' formulations. Applicants further point to the results of the comparative tests attached hereto that demonstrate that, e.g. BHT, which was also mentioned in DE '287, precipitates in commonly used amounts.

Cevc does not remedy these deficiencies in DE'287. Rather, Cevc is directed to transfersomal systems and is silent with respect to antioxidants and microbicides.

US '685 also does not remedy these deficiencies in DE'287 and Cevc. As previously discussed, US'685, among things, does not at all relate to systems comparable with the present transfersome systems, but, rather, to W/O creams which are completely different than the transfersome systems taught by applicants. Further, US '685 fails to mention the use of antioxidants and microbicides or which and how much of each substance may be successfully used without upsetting the well-balanced system of applicants' formulations.

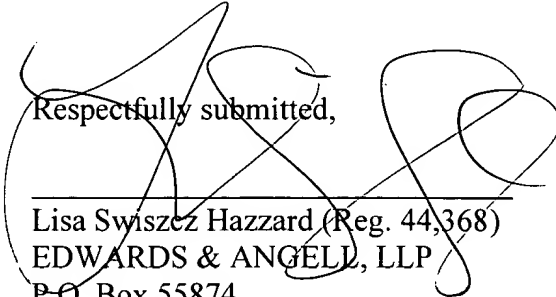
Accordingly, Applicants submit that claim 1 is patentable over DE'287, Cevc and US'685. Claims 2, 3, 5, 6, 12-14, 21-24, 35, 39-41, 44-46, 51, 54, 76, 83 and 86-90 depend from claim 1 and, likewise, are patentable over DE'287, Cevc and US'685. Claims 9, 84 and 85 have been canceled and, thus, rejection of these claims is moot. Reconsideration and withdrawal of the rejections is respectfully requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited. Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

If for any reason a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge or credit Deposit Account No. 04-1105 under order no. 58069 (47126).

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Respectfully submitted,



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